Asian Journal of Andrology (2014) 16, 372–377
© 2014 AJA, SIMM & SJTU. All rights reserved 1008-682X
www.asiaandro.com; www.ajandrology.com

Open Access

INVITED REVIEW

Prostate Cancer

Anti-angiogenesis in prostate cancer: knocked down but not out

Marijo Bilusic, Yu-Ning Wong

Angiogenesis is a very complex physiological process, which involves multiple pathways that are dependent on the homeostatic balance between the growth factors (stimulators and inhibitors). This tightly controlled process is stimulated by angiogenic factors, which are present within the tumor and surrounding tumor-associated stromal cells. The dependence of tumor propagation, invasion and metastasis on angiogenesis makes the inhibitors of new blood vessel formation attractive drugs for treating the malignancies. Angiogenesis can be disrupted by several distinct mechanisms: by inhibiting endothelial cells, by interrupting the signaling pathways or by inhibiting other activators of angiogenesis. This strategy has shown therapeutic benefit in several types of solid tumors, leading to Food and Drug Administration (FDA) approval of anti-angiogenic agents in the treatment of kidney, non-small cell lung, colon and brain cancers. Although no angiogenesis inhibitors have been approved for patients with metastatic prostate cancer, therapies that target new blood vessel formation are still an emerging and promising area of prostate cancer research.
Asian Journal of Andrology (2014) **16**, 372–377; doi: 10.4103/1008-682X.125903; published online: 08 April 2014

Keywords: angiogenesis; clinical trials; prostate cancer

INTRODUCTION

Angiogenesis is the process of new blood vessel formation and it is a normal process in growth, in wound healing and in the formation of granulation tissue; however, it is also crucial step for cancer growth, invasion and metastasis. Because tumor is dependent on the diffusion of nutrients and oxygen supply, establishing a sufficient blood supply is critical and limiting step for continued tumor progression.[1] As the cancer progresses and cells in the center of the tumor become more hypoxic, the tumor activates neo-angiogenesis process by shifting the homeostasis between angiogenesis inhibitors and stimulators, the process known as 'angiogenic switch'.[2] This switch can occur at different stages of the tumor development as result of metabolic stresses such as acidosis, inflammation, or hypoxia. In addition, pro- and anti-angiogenic factors are not only produced by tumor cells, but also by stromal cells of the tumor microenvironment, which as well plays an important role in tumor development by modulating the tumor's progression and metastasis.[3] Tumor vessels that are eventually formed are different compared with normal vasculature: they are disorganized with irregular structure and with altered interaction between endothelial cells.[4] Once cancer cells generate their own blood supply, they are capable of further invasion and have the capacity to metastasize. Folkman[5], in 1971 proposed the hypothesis that cancer growth is dependent on the formation of new blood vessel, which was repeatedly confirmed by multiple clinical studies with several angiogenesis inhibitors.[6] Although the most well-described angiogenic factor is the vascular endothelial growth factor (VEGF), several others angiogenic stimulators mainly receptor tyrosine kinase ligands[7] such as fibroblast growth factors (FGFs), angiopoeitin-1, epidermal growth factor (EGF), platelet-derived growth factor (PlGF), placental growth factor (PGF) and lysophosphatic acid (LPA) have been described. On the other hand, angiogenesis is inhibited by several angiogenic inhibitors such as angiostatin, endostatin, fumagillin, and matrix metalloproteinase inhibitors (MMPs). The balance between angiogenesis activators and inhibitors and the eventual changes in angiogenic equilibrium determine the state of the angiogenic switch.

The vast majority of anti-angiogenic agents being tested in the clinic are based on the strategies that either interfere with pro-angiogenic ligands or block the signaling of pro-angiogenic receptor tyrosine kinases. Also, inhibition of tumor growth in experimental animals can be achieved by means of selective inhibition of VEGF using anti-VEGF monoclonal antibodies (MoAbs), VEGF receptor small molecule kinase inhibitors, or soluble VEGF receptors.[8] All of these strategies have resulted in the inhibition of angiogenesis in several types of tumors, which is consistent with the hypothesis that tumor growth may be angiogenesis-dependent, regardless of the origin of the tissue. The disruption of the process of angiogenesis with novel molecules is an emerging and exciting area of clinical investigation in multiple cancer types, including prostate cancer.

ANGIOGENESIS AND PROSTATE CANCER

There is a growing body of literature suggesting that angiogenesis is playing an important role in prostate cancer. It has been reported that prostate cancer cells express VEGF[9] and that its expression is greater than that found in normal prostate tissue. The serum levels of the VEGF were found to be significantly higher in prostate cancer patients with metastatic disease compared with those not affected with metastatic disease.[10] Moreover, studies have found a correlation between the VEGF levels in blood and urine in prostate cancer patients and survival.[11]

Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA.
Correspondence: Dr. YN Wong (yu-ning.wong@fccc.edu)
Received: 29 October 2013; Revised: 09 December 2013; Accepted: 09 December 2013

Microvessel density, a histological measure of new blood vessel formation within a tumor, has been shown to correlate with Gleason score and may predict clinical or biochemical recurrence.[12] However, other studies have yet to confirm that microvessel density can be used as an independent prognostic factor.[13] In addition, studies have found that hypoxia can upregulate the expression of VEGF in prostate cancer[14] and that the hypoxia-inducible factor-1 (HIF-1), a key regulator responsible for survival of cells in hypoxic condition and the mediator of VEGF expression, has higher expression in prostate cancer cells compared with benign prostate cells.[15] Finally, some studies have demonstrated that *in vivo* alterations of testosterone levels regulate the expression of FGF, VEGF, and angiopoietin-family members.[16] Inhibition of angiogenesis, alone or in combination with chemotherapy, has potential antitumor efficacy against metastatic prostate cancer, and several anti-angiogenic agents have been tested in phase III of clinical trials or are currently undergoing testing in clinical trials (**Table 1** and **Table 2**).

LESSONS LEARNED FROM COMPLETED CLINICAL TRIALS OF ANTI-ANGIOGENIC AGENTS IN PROSTATE CANCER

None of the completed phase III clinical trials of anti-angiogenic agents performed to date met expectations to extend the life in men affected with metastatic prostate cancer. The results of early phase studies delivered great expectations for anti-angiogenesis treatment alone or in combination with cytotoxic chemotherapy in prostate cancer patients; however, that could not be confirmed in the randomized clinical trials. Experience in over a decade's of worth clinical trials have identified some of the key challenges in clinical development of anti-angiogenic agents in prostate cancer. Taken together, results of anti-angiogenic studies in prostate cancer demonstrated the need for better clinical trial endpoints and markers of clinical benefit.

What is the appropriate clinical trial endpoint?

Historically, overall survival (OS) has been considered the 'gold standard' for evaluating novel treatments in oncology, because of its objectivity; however, the use of OS as an endpoint is increasingly difficult given the long survival of prostate cancer patients and the additional survival benefit associated with novel therapies such as abiraterone, sipuleucel-T and enzalutamide that patients may receive after disease progression. Progression free survival (PFS) may be a surrogate endpoint that can be met earlier and shorten the time for drug development; however, PFS is not considered an ideal endpoint to the treatment as it may or may not necessarily translate into an OS improvement.[17] Potential measures of progression can include changes in prostate specific antigen (PSA), clinical status and/or imaging. These evaluations may not always correlate with each other, or with activity of the disease. Detection of progression cannot be predicted as clinically relevant since the progression is affected by the timing and frequency of assessments. In addition, investigators may differ in their interpretation of bone scan results or clinical progression. Definitions for PSA progression have been proposed by the PSA Working Group (PSAWG). To avoid misclassification of bone scan flares at the first assessment, the PSAWG2 recommends that the patients treated with non-cytotoxic drugs found to have new lesions noted on their first scan receive a second confirmatory scan after six weeks. They would be considered to have progressed if they have two additional lesions noted on the confirmatory scan. PSAWG further recommends a modification to Response Evaluation Criteria In Solid Tumors (RECIST), such that the only changes in lymph nodes were reported to be 2 cm or greater at baseline.[18,19] However, these guidelines have not been prospectively validated. In an attempt to identify intermediate clinical endpoints in prostate cancer trials, Halabi and colleagues[20] performed a pooled analysis of nine cancer and leukemia group B (CALGB) trials conducted from 1991 to 2004 that included 1296 chemotherapy naïve patients with castrate resistant prostate cancer (CRPC). They reported that PSA biochemical progression at six months and PFS at three and six months may predict OS, but those results needed to be prospectively validated. An analysis of SWOG 9916 clinical trial which evaluated the use of docetaxel in metastatic CRPC found that biochemical response (30% decline in PSA at 3 months) was found to be a predictive of OS.[21] The search for the ideal surrogate endpoint(s) for OS of prostate cancer that can shorten the time to complete prostate cancer clinical trials is still ongoing.

Novel mechanisms of action may not be measured by current standards of progression

The above mentioned analyses that measured the association between the PFS or biochemical responses were conducted using older studies of chemotherapy naive CRPC and may not be appropriate for novel therapies. For example, sipuleucel-T did not improve response rate, delay progression or cause reductions in PSA, as compared to placebo; however, this immunotherapy treatment demonstrated the improvement in OS.[22] In addition, PSA may not be an appropriate indicator of activity by the targeted agents. In a Phase II study of cabozantinib (described below), PSA did not correlate with radiologic changes in bone or soft tissue.[23] Preclinical studies using LNCaP prostate cancer cell lines treated with sorafenib demonstrated the inhibition of cancer cell growth while exhibiting simultaneous PSA increase, suggesting that PSA may not be an appropriate biomarker of sorafenib anticancer activity (discussed below).[24] In addition, clinical studies of sorafenib have also suggested PSA may not be an indicator of its activity in advanced prostate cancer patients.[24]

Toxicity

Given the advanced age of most men with prostate cancer, careful attention to toxicity profiles is especially important. Novel treatments, including the inhibitors of angiogenesis described in this review can be associated with toxicities such as hypertension, edema, thromboembolic events and bleeding. Therefore, it is possible that a drug may improve PFS but not OS if it causes excess toxicity.

Completed clinical trials of anti-angiogenic agents in prostate cancer

Bevacizumab

Bevacizumab (Avastin®; Genentech, San Francisco, CA, USA) is a recombinant, humanized monoclonal antibody that blocks angiogenesis by inhibiting VEGF-A. It is FDA approved for treatment of several malignancies including colorectal carcinoma, metastatic renal cell carcinoma, non-squamous non-small cell lung cancer, and recurrent glioblastoma. In a phase II study, 15 patients with chemotherapy naïve metastatic CRPC was treated with single agent bevacizumab 10 mg kg^{-1} IV every 14 days. Results showed no objective responses and only 4 patients (27%) had PSA decline less than 50%. The trial was halted for futility;[25] however, several future trials suggested potential activity when bevacizumab was combined with chemotherapy in patients with CRPC.

CALGB 90006 was a phase II trial that enrolled 79 patients who received docetaxel 70 mg m^{-2} IV, bevacizumab 15 mg kg^{-1} IV every three weeks with estramustine 280 mg TID on days one through five. Seventy seven patients were evaluable and received a median of eight cycles; Of the total 77 patients, 58 patients (75%) had a 50% PSA decline. Twenty–three of 39 patients with measurable disease had a partial response

Table 1: Completed phase III clinical trials of anti-angiogenic agents in prostate cancer

Drug	*NCT*	*Number of patients*	*Primary end point*	*Results*	*Toxicity*
Docetaxel with or without bevacizumab (CALGB 90401)[27]	NCT00110214	1050	OS	Negative study	Treatment related deaths (4.0% *vs* 1.2%, *P*=0.005)
Docetaxel with or without Aflibercept (VENICE)[38]	NCT00519285	1224	OS	Negative study	Treatment-related deaths (3.4% *vs* 1.5%)
Docetaxel with or without Lenalidomide (MAINSAIL)[44]	NCT00988208	1059	OS	Negative study (stopped early)	Increased
Prednisone with or without sunitinib[34] (post docetaxel)	NCT00676650	873	OS	Negative study (stopped early)	Increased

OS: overall survival

Table 2: Ongoing phase III clinical trials of anti-angiogenic agents in prostate cancer

Drug	*NCT*	*Number of patients*	*Primary end point*
Cabozantinib (COMET 1) previously treated mCRPC	NCT01605227	960	OS
Cabozantinib (COMET 2) previously treated mCRPC	NCT01522443	246	Pain response
Tasquinimod (completed enrolment)	NCT01234311	1200	PFS

OS: overall survival; PFS: progression free survival; mCRPC: metastatic castrate resistant prostate cancer

(PR) (59%). PFS was 8.0 months with a median OS of 24 months. The most common severe toxicities were neutropenia (69%), fatigue (25%), thrombosis and embolism (9%).[26] This study did not meet its primary endpoint of PFS; however, observed anti-tumor activity and favorable OS led to a phase III study of bevacizumab with docetaxel chemotherapy.

CALGB 90401 was a phase III study that randomized 1050 patients to docetaxel (75 mg m^{-2} IV every 3 weeks) with 10 mg of daily prednisone with or without 15 mg kg^{-1} bevacizumab. The primary endpoint of this study was OS, and secondary endpoints were PFS, objective response (OR) and 50% decline in PSA. The addition of bevacizumab did not improve OS despite the improvement in OR and PFS. The median OS was similar between the two arms: 22.6 months in bevacizumab group *vs* 21.5 months in control group (HR 0.91; P = 0.181). Also, the addition of bevacizumab was associated with greater treatment toxicity (Grade ≥3 neutropenia, leukopenia, hypertension, fatigue, gastro-intestinal bleeding and perforation) and the significantly higher number of treatment related deaths (4.0% *vs* 1.2%; P = 0.005).[27] OS in the control group was longer than reported in other trials,[28] raising questions that the study may have been underpowered or that patients were enrolled earlier in their disease course which could lead to a lead-time bias. Interestingly, recent results from a phase III clinical trial in metastatic colorectal carcinoma (ML18147) showed that maintenance of bevacizumab with standard chemotherapy in patients beyond disease progression has improved the OS[29] suggesting that duration of anti-angiogenic treatment may be important and that the mechanism of resistance to anti-VEGF agents may be different. The prostate cancer trials described above did not continue bevacizumab treatment that was beyond the disease progression.

Sorafenib

Sorafenib (Nexavar®, Bayer HealthCare and Onyx Pharmaceuticals, Emeryville, CA, USA) is a small molecule tyrosine kinase inhibitor (TKI) which targets RAF kinase in addition to VEGF receptor 2 (VEGFR-2) and platelet derived growth factor receptor beta (PDGFR-beta) resulting in antiangiogenic effects. The agent is FDA approved for hepatocellular carcinoma and renal cell carcinoma. Sorafenib has been evaluated in phase II studies in patients with CRPC both prior to and following docetaxel chemotherapy. Dahut and colleagues[24] reported results of a single arm study of sorafenib given at 400 mg daily. Initial results from the first 22 patients with CRPC following docetaxel chemotherapy showed no PSA declines that was greater than 50%. Of the 21 patients with progressive disease, 13 had PSA progression only with stable disease (defined by clinical and radiographic criteria). The second part of the study enrolled 24 additional patients (21 previously treated with docetaxel chemotherapy with a median Gleason score of 8). Ten patients had stable disease and one patient had PR. Median PFS (defined by clinical or radiographic criteria) was 3.7 months and median OS was 18.0 months. Pooled data from both stages of the trial (N = 46) demonstrated a median OS of 18.3 months. Reported toxicities were grade 2 and 3 hand-foot skin reaction, rash, transaminitis, and fatigue.[30]

Another phase II trial enrolled 57 chemotherapy naïve CRPC patients who were treated with sorafenib 400 mg BID. Of the 55 evaluable patients, only two had PSA decline of more than 50% and none had objective responses based on RECIST criteria. Interestingly 15 patients had stable disease and 31% of patients had not progressed by 12 weeks.[31] Chi reported phase II findings in 2008 with 28 chemotherapy naïve CRPC patients. Only 3.6% of patients had PSA decline more than 50%, interestingly more patients had PSA decline after treatment discontinuation indicating that treatment with sorafenib may have caused increased PSA levels independent of tumor growth.[32]

Sunitinib

Sunitinib (Sutent®, Pfizer Inc. New York, NY, USA) is an oral multi TKI with activity against VEGFR-2, PDGFRb, FLT-3 and KIT, which play a role in tumor angiogenesis and tumor cell proliferation. It is FDA approved in advanced renal cell carcinoma and gastrointestinal stromal tumor (GIST) after failure of imatinib. Sunitinib has being studied with docetaxel in several clinical trials. Zurita completed a phase I/II trial of sunitinib combined with docetaxel and prednisone in 55 chemotherapy naïve CRPC patients. Patients received sunitinib at 37.5 mg per day on days 1–14, docetaxel 75 mg m^{-2} on day one and prednisone 5 mg BID. The primary endpoint of the study was PSA decline by PSAWG-1 criteria. Of the 55 chemotherapy naïve CRPC patients, 56% of the patients had PSA decline; 39% of the patients had a partial response with median time to progression (TTP) of 42 weeks. Median PFS and OS were 12.6 and 21.7 months, respectively. Only 22% patients competed the planned 16 cycles of treatment, 36% discontinued for disease progression while 27% discontinued due to adverse events, most commonly grade 3 and 4 neutropenia (75%), grade 3 and 4 febrile neutropenia (15%) and fatigue (15%).[33]

A randomized, multicenter phase III trial comparing sunitinib and prednisone with prednisone alone in CRPC patients who have failed docetaxel-based therapy was halted for lack of efficacy after the planned interim analysis in September 2010. This trial randomized a total of 873 men, median age of 68 years, to sunitinib (N = 584) or placebo (N = 289). The median treatment duration was 3.7 months on the sunitinib arm and 3.4 months on the placebo arm. OS was similar in both groups (13.1 *vs* 11.8 months; HR 0.91; P = 0.168); however, PFS was significantly longer on the sunitinib arm (5.6 *vs* 4.1 months; HR 0.73; P < 0.001).[34]

Aflibercept

Aflibercept (Zaltrap®, ziv-aflibercept; Sanofi, Paris, France; and Regeneron, Tarrytown, NY, USA) is a recombinant fusion protein consisting of extracellular domains of the human VEGF receptor (VEGFR) fused to the Fc portion of human immunoglobulin G1. Aflibercept has binding affinity to the isoform VEGF-A, VEGF-B and platelet-derived growth factors PlGF1 and PlGF2, thereby inhibiting angiogenesis.[35] It is FDA approved for the treatment of patients with metastatic colorectal cancer that is resistant or has progressed following an oxaliplatin-based regimen.[36] Aflibercept has been tested in phase I and II clinical trials with docetaxel[37] although no phase II trials of this combination have been done in patient with metastatic CRPC.

VENICE was a phase III, multicentre, randomized double-blind placebo-controlled study, which enrolled 1224 chemotherapy naïve patients with metastatic CRPC. Study randomized 1224 patients to docetaxel (75 mg m^{-2} IV every 3 weeks) and prednisone (5 mg BID) plus aflibercept (6 mg kg^{-1} IV every 3 weeks) or to docetaxel, prednisone and placebo. There was no improvement in OS in the aflibercept group (22.1 *vs* 21.2 months, HR 0.94; P = 0.38). In addition, there was statistically significant increased number of side effects in the aflibercept arm (grade 3 and 4 gastrointestinal symptoms (30% *vs* 8.0%), hypertension (13% *vs* 3.3%), bleeding (5.2% *vs* 1.7%), fatigue (16% *vs* 7.7%), infections (20% *vs* 10%) and treatment-related fatal adverse events (3.4% *vs* 1.5%).[38]

Thalidomide and lenalidomide

Thalidomide (Thalomid®, Celgene Corporation, Summit, NJ, USA) is an oral synthetic glutamic acid derivative with teratogenic, immunomodulatory and anti-angiogenic activities. Its mechanism of action is still not clearly understood. It inhibits the production of tumor necrosis factor alpha (TNF-alpha), basic fibroblast growth factor (bFGF) and VEGF causing inhibition of angiogenesis.[39] It is FDA approved for newly diagnosed multiple myeloma. It has been evaluated alone or in combination with cytotoxic agents in prostate cancer. A phase II trial of 100 mg daily of thalidomide in CRPC patients demonstrated >50% PSA decline in 3 out of 20 (15%) of patients.[40] A phase II randomized study tested the docetaxel (30 mg m^{-2} IV weekly for 3 weeks on 28-day cycles) with or without thalidomide (200 mg daily). In an updated analysis with median follow-up of 46.7 months, the median OS for the combined arm was 25.9 months *vs* 14.7 months for docetaxel alone, which was statistically significant (P = 0.04). Thromboembolic events occurred in 12 of the first 43 patients. Following this event, prophylactic anticoagulation with low-molecular weight heparin was given in the combination arm. Other toxicities in the combined arm were manageable (fatigue, neuropathy, depression and pleural effusions).[41]

Lenalidomide (Revlimid®, Celgene Corporation, Summit, NJ, USA) is a thalidomide analog. It inhibits TNF-alpha production, promotes G1 cell cycle arrest and apoptosis of malignant cells and reduces serum levels of the VEGF and bFGF. It is FDA approved for newly diagnosed multiple myeloma, mantle cell lymphoma and low or intermediate-1 risk myelodysplastic syndromes (MDS). In phase I/II clinical trials, lenalidomide demonstrated activity and tolerability in prostate cancer patients when used as a single agent[42] or in combination with docetaxel and prednisone.[43] These results provided the basis for a randomized phase III clinical trial of lenalidomide in combination with docetaxel and prednisone as first-line therapy for metastatic CRPC (MAINSAIL trial). Eligible patients were randomized to docetaxel 75 mg m^{-2} on day one, and prednisone 5 mg BID plus lenalidomide 25 mg daily, or to docetaxel, prednisone and placebo. The primary endpoint was OS, and key secondary endpoints were overall response rate (ORR), PFS, and safety. The study enrolled a total of 1059 patients, but was discontinued on the recommendations of the Data Monitoring Committee. The median OS was shorter in the lenalidomide arm (77 weeks) and had not been reached in the placebo group (HR 1.53, P = 0.0017). Median PFS was 45 weeks with lenalidomide and 46 weeks with placebo (HR 1.32, P = 0.0187). In addition, patients randomized to lenalidomide arm had significantly higher rates of febrile neutropenia and other non-hematological toxicities.[44]

Dual anti-angiogenic blockade (thalidomide and bevacizumab)

Dual anti-angiogenic therapy (bevacizumab and thalidomide) in combination with docetaxel and prednisone has also been evaluated in patients with metastatic CRPC. A phase II trial reported 90% biochemical response rate and ORR in measurable disease of 64%. The median OS was 28.4 months, which was longer than the historical controls.[28] However, this combination therapy was very toxic. All patients developed grade 3 and 4 neutropenia, 20% had grade 3 and 4 thrombocytopenia or anemia. Grade 3 and 4 non-hematologic toxicities occurring in more than 10% of the patients were syncope and hypertension. Significant thalidomide-related toxicities were constipation (55%), fatigue (35%), peripheral neuropathy (13%), and depression (10%). Grade 2 osteonecrosis of the jaw occurred in 18.3% of patients, much higher than the previously reported data.[45]

ONGOING PHASE III CLINICAL TRIALS OF ANTI-ANGIOGENIC AGENTS IN PROSTATE CANCER

Cabozantinib

Cabozantinib (Cometriq®, XL184, Exelixis, San Francisco, CA, USA) is an orally bioavailable dual TKI with strong activity against VEGF receptor 2 (VEGFR2) and c-MET. It is FDA approved for the treatment of medullary thyroid carcinoma. c-MET is also expressed in prostate cancer tissue.[46] Based on the broad activity demonstrated in several phase I trials, a phase II randomized discontinuation trial was conducted in nine selected tumor types including CRPC. One hundred and seventy-one men with CRPC were enrolled. Seventy-two percent demonstrated regressions in soft tissue metastases, and 68% of patients showed significant improvement on bone scans, including CR in 12% of evaluable patients. The ORR at 12 weeks was 5%, with SD in 75% patients. The median PFS was 23.9 weeks for patients who were previously treated with a docetaxel chemotherapy (N = 74) and 29.7 weeks for chemo naïve patients (N =97).[23] Interestingly, the improvements in bone metastasis were accompanied by improvement in serum markers associated with bone destruction (c-telopeptide and alkaline phosphatase) and by pain improvement in 67% of patients. More than half of the patients enrolled in the study had significant toxicity, mostly fatigue, and several gastrointestinal symptoms including constipation, diarrhea, nausea and decreased appetite. A recent study tested a lower dose of cabozantinb (40 mg) and found that the drug had similar clinical effect but less toxicity.[47]

Two phase III studies are currently underway in patients with CRPC affected by bone metastases who have received prior docetaxel and abiraterone or enzalutamide (COMET - Cabozantinib MET Inhibition CRPC Efficacy Trial 1 (NCT01605227) and 2

(NCT01522443). COMET-1 randomizes patients to cabozantinib *vs* prednisone and evaluates OS, whereas the COMET-2 randomizes patients to cabozantinib *vs* mitoxantrone and evaluates the durability of pain response (**Table 2**).

Tasquinimod

Tasquinimod (ABR-215050, Active Biotech, Lund, Sweden) is a quinoline-3-carboxamide linomide analog with anti-angiogenic and potential anticancer activities. Tasquinimod has been shown to decrease blood vessel density but the exact mechanism of action is still unclear.[48] It is presumed to have an anti-angiogenic effect by downregulating hypoxia-inducible factor-1α and by inhibiting myeloid-derived suppressor cells (MDSC), which play an important role during angiogenesis. Interestingly, it was also found to be an inhibitor of S1900A9, which is expressed on MDSC and in the tumor microenvironment, and has been postulated to have a role in immune suppression. A phase II study randomized 206 patients with metastatic CRPC to tasquinimod *vs* placebo. Median PFS was 7.6 *vs* 3.3 months ($P = 0.0042$). The treatment was well tolerated; the most common side effects were fatigue, nausea and inflammation. There were few rare but serious adverse events including hyperamylasemia, sinus tachycardia and stroke.[49] A randomized, double-blind, placebo-controlled phase III clinical trial in men with metastatic CRPC recently completed the enrollment (1200 patients) (NCT01234311). The final results of the trial are not yet available (**Table 2**).

OTHER ANTI-ANGIOGENIC AGENTS CURRENTLY UNDER EVALUATION IN PROSTATE CANCER

Cediranib

Cediranib (Recentin®, AZD2171, AstraZeneca, London, UK) is an oral small molecule inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3 and also of PDGF receptor and c-kit.[50] Cediranib has been reported to have activity in prostate cancer. A phase I trial reported a maximum tolerated dose of 20 mg with dose-limiting toxicities of muscle weakness and hypertension.[51] It was studied in a phase II study of 59 patients of which two thirds were heavily pretreated with two or more previous chemotherapy regimens. This study met its primary endpoint. Six of 39 patients with measurable disease had partial responses. At six months, 43.9% of patients were progression free; the median PFS and OS were 3.7 months and 10.1 months, respectively. The most frequent adverse events were fatigue, anorexia, weight loss and hypertension. The addition of prednisone reduced the incidence of toxicities.[52] A phase II study investigating the use of cediranib with dasatinib in patients with docetaxel-refractory metastatic CRPC is currently underway (NCT01260688). Another phase II study is evaluating docetaxel with or without cediranib in chemotherapy-naïve patients with CRPC (NCT00527124).

TRC105

TRC105 (Tracon Pharmaceuticals, San Diego, CA, USA) is a therapeutic human/murine chimeric monoclonal antibody to CD105 (endoglin), a TGF-β accessory receptor that is highly expressed on tumor vessel of endothelial cells and appears to be essential during angiogenesis by altering TGF-β and BMP-9 signaling. By binding to CD105, TRC105 may inhibit angiogenesis. Recently reported results of the phase I study demonstrated some evidence of clinical activity in advanced solid tumors. A phase I study enrolled 50 patients with advanced solid tumors who were treated with escalating doses of TRC105. Twenty-one of the 45 evaluable patients (47%) had stable disease at 2 months and 6 of 44 were progression free at 4 months including two ongoing responses at 48 and 18 months. The safety profile of TRC105 appears to be distinct from other VEGF inhibitors; it was well tolerated with common toxicities such as anemia, infusion reactions and telangiectasia.[53] An ongoing clinical trial is testing TRC 105 as a single agent in metastatic CRPC (NCT01090765).

Trebananib

Trebananib (AMG 386, Amgen, Thousand Oaks, CA, USA) is a novel peptide-Fc fusion protein that disrupts tumor endothelial cells proliferation and angiogenesis by preventing interaction between angiopoietins (Ang) 1 and 2 and Tie2 receptors. A phase I study enrolled 32 patients and demonstrated some evidence of clinical activity in advanced solid tumors. Four patients had stable disease at 16 weeks, whereas one ovarian cancer patient had a durable partial response after 156 weeks. Trebananib was well tolerated; the most commonly observed adverse events were peripheral edema, fatigue and proteinuria.[54] A phase I/II study investigating the use of abiraterone with or without trebananib in patients with chemotherapy naive metastatic CRPC is currently underway (NCT01553188).

CONCLUSIONS

While targeting angiogenesis appears to be a rational therapeutic approach for metastatic CRPC, there are still major obstacles in identifying the appropriate timing and patients that may benefit from these agents. Several phase III trials of anti-angiogenic agents were discouraging; however, anti-angiogenic agents are not out (yet). The role that anti-angiogenic agents have in metastatic CRPC, still remains to be evaluated with tasquinimod and cabozantinib being evaluated in phase III clinical trials along with several other angiogenesis inhibitors in Phase II studies. Forthcoming results from these clinical trials will hopefully clarify the role of angiogenesis inhibitors in the prostate cancer.

There are several challenges in drug development for this class of agents. Previously used measures of treatment affect (PFS, PSA response) may not be appropriate for angiogenesis inhibitors. The development of biomarkers of anti-tumor and anti-angiogenic activity, including novel imaging modalities may help to clarify the true activity of these drugs. In addition, these treatments must have acceptable safety profiles, given the advanced age of presentation for many men with prostate cancer. The role of combination therapies may also be explored, with early evaluation for both safety and efficacy.

AUTHOR CONTRIBUTIONS

MB and YNW both drafted the manuscript. Both authors read and approved the final manuscript.

COMPETING INTERESTS

MB has no competing financial interests. YNW has received grant support from Pfizer.

ACKNOWLEDGMENTS

The work was supported by Award Number P30CA006927 from the National Cancer Institute.

REFERENCES

1 Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol* 1995; 146: 1029–39.
2 Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* 1996; 86: 353–64.
3 Eccles SA, Welch DR. Metastasis: recent discoveries and novel treatment strategies. *Lancet* 2007; 369: 1742–57.
4 Folkman J. Angiogenesis. *Ann Rev Med* 2006; 57: 1–18.
5 Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971; 285: 1182–6.
6 Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; 1: 27–31.
7 Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Med* 2000; 6: 389–95.

8 Morabito A, De Maio E, Di Maio M, Normanno N, Perrone F. Tyrosine kinase inhibitors of vascular endothelial growth factor receptors in clinical trials: current status and future directions. *Oncologist* 2006; 11: 753–64.
9 Ferrer FA, Miller LJ, Andrawis RI, Kurtzman SH, Albertsen PC, *et al*. Vascular endothelial growth factor (VEGF) expression in human prostate cancer: *in situ* and *in vitro* expression of VEGF by human prostate cancer cells. *J Urol* 1997; 157: 2329–33.
10 Duque JL, Loughlin KR, Adam RM, Kantoff PW, Zurakowski D, *et al*. Plasma levels of vascular endothelial growth factor are increased in patients with metastatic prostate cancer. *Urology* 1999; 54: 523–7.
11 George DJ, Halabi S, Shepard TF, Vogelzang NJ, Hayes DF, *et al*. Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on Cancer and Leukemia Group B 9480. *Clin Cancer Res* 2001; 7: 1932–6.
12 Gettman MT, Pacelli A, Slezak J, Bergstralh EJ, Blute M, *et al*. Role of microvessel density in predicting recurrence in pathologic stage T3 prostatic adenocarcinoma. *Urology* 1999; 54: 479–85.
13 Weidner N, Carroll PR, Flax J, Blumenfeld W, Folkman J. Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol* 1993; 143: 401–9.
14 Cvetkovic D, Movsas B, Dicker AP, Hanlon AL, Greenberg RE, *et al*. Increased hypoxia correlates with increased expression of the angiogenesis marker vascular endothelial growth factor in human prostate cancer. *Urology* 2001; 57: 821–5.
15 Du Z, Fujiyama C, Chen Y, Masaki Z. Expression of hypoxia-inducible factor 1alpha in human normal, benign, and malignant prostate tissue. *Chin Med J* 2003; 116: 1936–9.
16 Wang GM, Kovalenko B, Huang Y, Moscatelli D. Vascular endothelial growth factor and angiopoietin are required for prostate regeneration. *Prostate* 2007; 67: 485–99.
17 Fallowfield LJ, Fleissig A. The value of progression-free survival to patients with advanced-stage cancer. *Nat Rev Clin Oncol* 2011; 9: 41–7.
18 Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, *et al*. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the prostate-specific antigen working group. *J Clin Oncol* 1999; 17: 3461–7.
19 Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, *et al*. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the prostate cancer clinical trials working group. *J Clin Oncol* 2008; 26: 1148–59.
20 Halabi S, Vogelzang NJ, Ou SS, Owzar K, Archer L, *et al*. Progression-free survival as a predictor of overall survival in men with castrate-resistant prostate cancer. *J Clin Oncol* 2009; 27: 2766–71.
21 Armstrong AJ, Garrett-Mayer E, Ou Yang YC, Carducci MA, Tannock I, *et al*. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 2007; 25: 3965–70.
22 Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, *et al*. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; 363: 411–22.
23 Smith DC, Smith MR, Sweeney C, Elfiky AA, Logothetis C, *et al*. Cabozantinib in patients with advanced prostate cancer: results of a phase ii randomized discontinuation trial. *J Clin Oncol* 2013; 31: 412–9.
24 Dahut WL, Scripture C, Posadas E, Jain L, Gulley JL, *et al*. A phase II clinical trial of sorafenib in androgen-independent prostate cancer. *Clin Cancer Res* 2008; 14: 209–14.
25 Reese David M, Fratesi P, Corry M, Novotny W, Holmgren E, *et al*. A phase II trial of humanized anti-vascular endothelial growth factor antibody for the treatment of androgen-independent prostate cancer. *Prostate J* 2001; 3: 65–70.
26 Picus J, Halabi S, Kelly WK, Vogelzang NJ, Whang YE, *et al*. A phase 2 study of estramustine, docetaxel, and bevacizumab in men with castrate-resistant prostate cancer: results from Cancer and Leukemia Group B Study 90006. *Cancer* 2011; 117: 526–33.
27 Kelly WK, Halabi S, Carducci M, George D, Mahoney JF, *et al*. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol* 2012; 30: 1534–40.
28 Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX327 study. *J Clin Oncol* 2008; 26: 242–5.
29 Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, *et al*. ML18147 Study Investigators. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 29–37.
30 Aragon-Ching JB, Jain L, Gulley JL, Arlen PM, Wright JJ, *et al*. Final analysis of a phase II trial using sorafenib for metastatic castration-resistant prostate cancer. *BJU Int* 2009; 103: 1636–40.
31 Steinbild S, Mross K, Frost A, Morant R, Gillessen S, *et al*. A clinical phase II study with sorafenib in patients with progressive hormone-refractory prostate cancer: a study of the CESAR Central European Society for Anticancer Drug Research-EWIV. *Br J Cancer* 2007; 97: 1480–5.
32 Chi KN, Ellard SL, Hotte SJ, Czaykowski P, Moore M, *et al*. A phase II study of sorafenib in patients with chemo-naive castration-resistant prostate cancer. *Ann Oncol* 2008; 19: 746–51.
33 Zurita AJ, George DJ, Shore ND, Liu G, Wilding G, *et al*. Sunitinib in combination with docetaxel and prednisone in chemotherapy-naive patients with metastatic, castration-resistant prostate cancer: a phase 1/2 clinical trial. *Ann Oncol* 2012; 23: 688–94.
34 Michaelson MD, Oudard S, Ou YC, Sengeløv L, Saad F, *et al*. Randomized, placebo-controlled, phase III trial of sunitinib plus prednisone versus prednisone alone in progressive, metastatic, castration-resistant prostate cancer. *J Clin Oncol* 2014; 32: 76-82.
35 Holash J, Davis S, Papadopoulos N, Croll SD, Ho L, *et al*. VEGF-Trap: A VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci* 2002; 99: 11393–8.
36 Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, *et al*. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; 30: 3499–506.
37 Isambert N, Freyer G, Zanetta S, You B, Fumoleau P, *et al*. Phase I dose-escalation study of intravenous aflibercept in combination with docetaxel in patients with advanced solid tumors. *Clin Cancer Res* 2012; 18: 1743–50.
38 Tannock IF, Fizazi K, Ivanov S, Karlsson CT, Fléchon A, *et al*. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. *Lancet Oncol* 2013; 14: 760–8.
39 Ng SS, MacPherson GR, Gütschow M, Eger K, Figg WD. Antitumor effects of thalidomide analogs in human prostate cancer xenografts implanted in immunodeficient mice. *Clin Cancer Res* 2004; 10: 4192–7.
40 Drake MJ, Robson W, Mehta P, Schofield I, Neal DE, *et al*. An open-label phase II study of low-dose thalidomide in androgen-independent prostate cancer. *Br J Cancer* 2003; 88: 822–7.
41 Dahut WL, Gulley JL, Arlen PM, Liu Y, Fedenko KM, *et al*. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol* 2004; 22: 2532–9.
42 Keizman D, Zahurak M, Sinibaldi V, Carducci M, Denmeade S, *et al*. Lenalidomide in nonmetastatic biochemically relapsed prostate cancer: results of a phase I/II double-blinded, randomized study. *Clin Cancer Res* 2010; 16: 5269–76.
43 Tohnya TM, Ng SS, Dahut WL, Wright JJ, Arlen PM, *et al*. Aphase I study of oral CC-5013 (lenalidomide, Revlimid), a thalidomide derivative, in patients with refractory metastatic cancer. *Clin Prostate Cancer* 2004; 2: 241–3.
44 Petrylak DP, Fizazi K, Sternberg C, *et al*. Phase 3 study to evaluate the efficacy and safety of docetaxel and prednisone with or without lenalidomide in patients with castrate-resistant prostate cancer (CRPC): The MAINSAIL trial. 2012 ESMO Congress. Abstract LBA24.
45 Ning YM, Gulley JL, Arlen PM, Woo S, Steinberg SM, *et al*. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2010; 28: 2070–6.
46 Pisters LL, Troncoso P, Zhau HE, Li W, von Eschenbach AC, *et al*. c-met proto-oncogene expression in benign and malignant human prostate tissues. *J Urol* 1995; 154: 293–8.
47 Lee RJ, Saylor PJ, Michaelson MD, Rothenberg SM, Smas ME, *et al*. A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. *Clin Cancer Res* 2013; 19: 3088–94.
48 Isaacs JT, Pili R, Qian DZ, Dalrymple SL, Garrison JB, *et al*. Identification of ABR-215050 as lead second generation quinoline-3-carboxamide anti-angiogenic agent for the treatment of prostate cancer. *Prostate* 2006; 66: 1768–78.
49 Pili R, Häggman M, Stadler WM, Gingrich JR, Assikis VJ, *et al*. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. *J Clin Oncol* 2011; 29: 4022–8.
50 Wedge SR, Kendrew J, Hennequin LF, Valentine PJ, Barry ST, *et al*. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. *Cancer Res* 2005; 65: 4389–400.
51 Ryan C, Stadler W, Roth B, Hutcheon D, Conry S, *et al*. Phase I dose escalation and pharmacokinetic study of AZD2171, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase, in patients with hormone refractory prostate cancer (HRPC). *Invest New Drugs* 2007; 25: 445–51.
52 Dahut WL, Madan RA, Karakunnel JJ, Adelberg D, Gulley JL, *et al*. Phase II clinical trial of cediranib in patients with metastatic castration-resistant prostate cancer. *BJU Int* 2013; 111: 1269–80.
53 Rosen LS, Hurwitz HI, Wong MK, Goldman J, Mendelson DS, *et al*. A phase I first-in-human study of TRC105 (Anti-Endoglin Antibody) in patients with advanced cancer. *Clin Cancer Res* 2012; 18: 4820–9.
54 Herbst RS, Hong D, Chap L, Kurzrock R, Jackson E, *et al*. Safety, pharmacokinetics, and antitumor activity of AMG 386, a selective angiopoietin inhibitor, in adult patients with advanced solid tumors. *J Clin Oncol* 2009; 27: 3557–65.

How to cite this article: Bilusic M, Wong YN. Anti-angiogenesis in prostate cancer: knocked down but not out. *Asian J Androl* 08 April 2014. doi: 10.4103/1008-682X.125903. [Epub ahead of print]